VENOUS THROMBOEMBOLISM

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Objectives

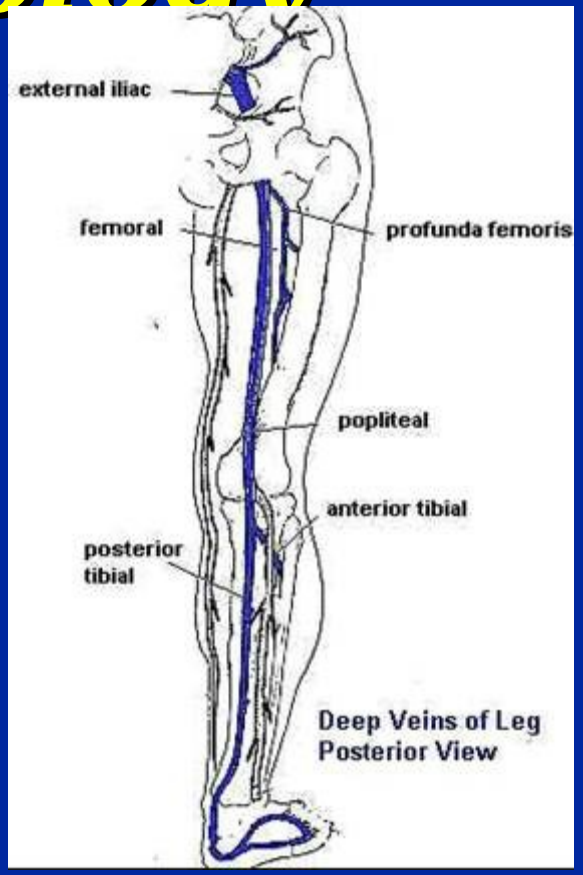
1. **To understand the role of diagnostic testing in the evaluation of Venous Thromboembolism**
2. **To understand the management options for Venous Thromboembolism**
3. **To understand the risk factors for Venous Thromboembolism to establish prevention strategies.**

Goals of Management

- Prevent mortality/morbidity from PE
- Prevent sequelae of venous insufficiency (post thrombotic syndrome)

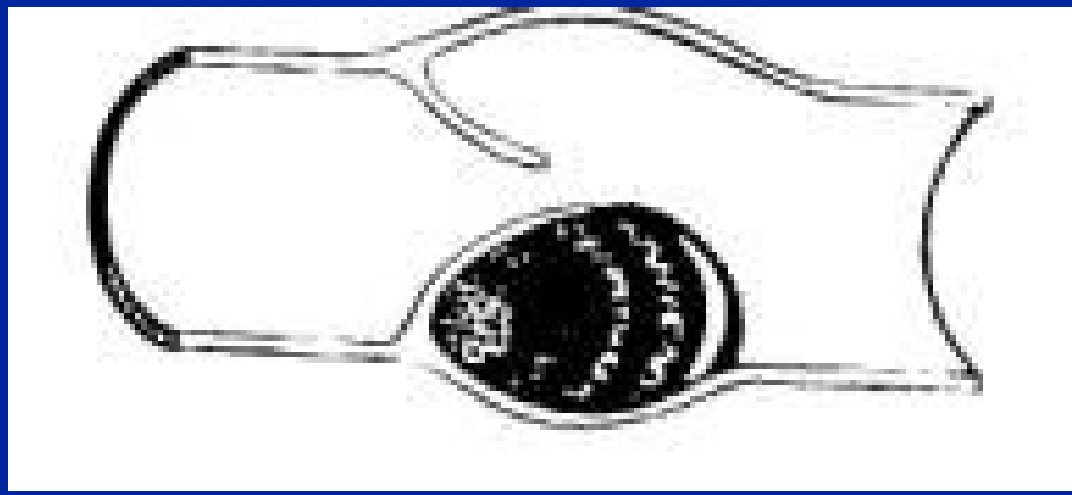
Deep Vein Thrombosis Epidemiology

- Over 600,000 hospitalizations per year
- Up to 50-70% proximal DVT's will result in PE (most asymptomatic)
- Common primary care diagnosis



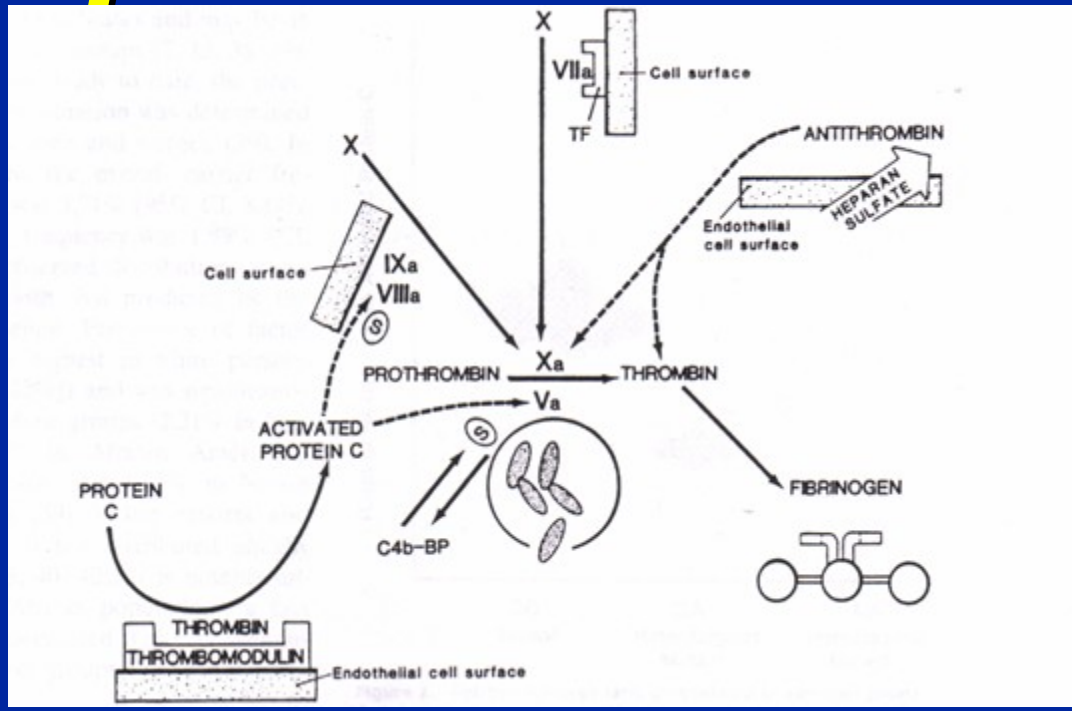
Risk Factors

- Virchow's Triad
  - Hypercoagulablity - OCP's, HRT, Hypercoagulable state
  - Stasis - Immobility, CHF, Obesity, Pregnancy, Air travel >4 hrs
  - Endothelial damage - Limb trauma, major surgery



Hypercoagulable State Thrombophilia

- Cancer -Pancreatic, Colonic, Urologic (mucin secreting)
- Deficiency of Protein C, Protein S, Antithrombin III, Prothrombin 20210A Mutation
- Hyperhomocysteinemia
- Anticardiolipin Antibody Syndrome
- Nephrotic Syndrome
- Myeloproliferative Disorders



Factor V Leiden

- **G1691A mutation**
  - **glutamine for arginine on Factor V**
- **Resistance to activated Protein C degradation**
- **Overall 3.71% prevalence**
- **Heterozygous Fe on OCP 35-50X increased risk of VTE**
- **Homozygous Fe on OCP several hundred fold increased risk of VTE**

Prothrombin 20210A Mutation

- **30% increased Prothrombin levels**
- **.7-6% prevalence**
- **Increased RR ~2.8**
- **Uncommon in non-white population**

Symptoms

- Leg pain with swelling in a high risk patient (usually unilateral)

Differential Diagnosis

- Knee
  - Baker's Cyst
  - DJD or injury
- Muscle Injury/Tear (Gastrocnemius)
- Cellulitis
- Edema in a paralyzed extremity
- Lymphedema/Lymph angitis
- Venous Insufficiency

Pretest Probability

Active cancer

Paralysis or casting

Recent immobilization or surgery

Tenderness along the deep veins

Swelling of the entire leg

Calf circumference diff > 3 cm

Pitting edema

No alternative dx

Distension of venous

al

0	low risk
1-2	mod risk
>2	high risk

Duplex Ultrasound

- **M**
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- **I**

Ann Int Med 1998 128(1):1

405 pts with first DVT

US day 0 and 5-7

3 month f/u

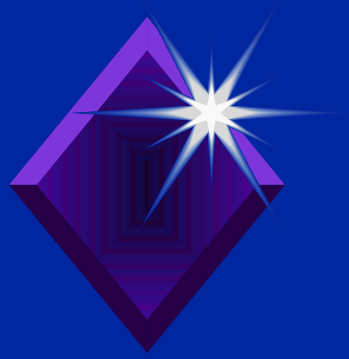
342 with initial nl and 7 abn at f/u

0 deaths for PE and 2 VTE @ 3months (0.6%)

repeat in 3-7 days

D-dimer

- Fibrin degradation product (FSP)
- Increased in DVT, PE, MI, sepsis, postpartum, metastatic cancer, CVD
- Not reliable if h/o Ca, age >70, or on Coumadin
- Level < 500ug/l considered negative
- NPV alone near 96%
- NPV near 100% if neg with low clinical suspicion



DVT Suspected

D-Dimer

Negative

Positive

Low/Mod Prob

High Prob

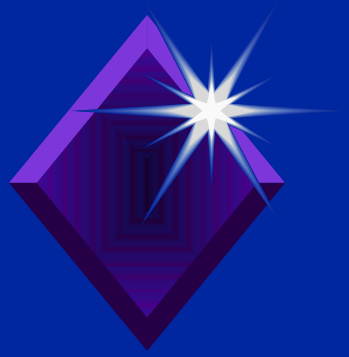
Ultrasound

Consider Repeat @ 7 days for persistent Sx and Mod or high risk

Treat

Magnetic Resonance Venography (MRV)

- No contrast material used (Gadolinium enhanced)
- More effective for pelvic vessels, head, neck
- Can differentiate old from new thrombus
- Can do legs or legs and lung simultaneously
- Sensitivity = 97%
- Specificity = 95%



Treatment

Traditional

- H
  (
- R
  d
  a

Arch Int Med 1997;157:305

95 pts (62 FFT and 28 occlusive thrombus)

Rx LMWH or Heparin

US, venogram, VQ then PAgram

PE

- 64% with FFT
- 50% occlusive

Recurrent PE

- 3.3% FFT
- 3.7% occlusive

Problems

- Does not preserve valves/valve function, therefore does not prevent chronic venous insufficiency
- Heparin side effects
- Risk of recurrent DVT
  - approx. 36%

Coumadin

- Coumadin starting day 1
- 4 day overlap with Heparin
- Duration of Coumadin therapy?
  - 1st episode 3 months
  - 2nd episode 1 year
  - 3rd episode indefinite
- To maintain INR 2-3
- Avg cost $0.55/day

Coumadin Side Effects

- INR adjustments based on diet, medications,…
- Early pro-coagulant effect - overlap 3-4 days with Heparin
  - Transient Protein C & S deficiency
- Hemorrhage 6-29%
- Purple Toes Syndrome
- Skin necrosis (usually early due to transient Protein C deficiency)
- Teratogenic

Coumadin Reversal

- FFP - rapid, but with blood product risk
- Vit K
  - Large dose (5-10 mg IV) makes re-anticoagulation difficult
  - Low dose (0.5-1 mg IV) will reduce INR in hrs
- Heparin window for high risk patients undergoing elective procedures

Heparin Side Effects

- **Hemorrhage 6%**
- **Heparin Associated Thrombocytopenia (HAT)**
  - **Platelet count <100,000 or >50% decrease over baseline after day 5**
  - **Platelet activation (PF 4)**
  - **Hypercoagulable state 7-10 days into treatment**
  - **Venous and arterial thrombi**
  - **Platelet activation factor (PAF)**

Low-Molecular-Weight Heparins LMWH

- Enzymatically fragmented heparins
- Enoxaparin (Lovenox)
- Dalteparin (Fragmin)
- Fraxiparine (Nadroparin)
- Logiparin (Tinzaparin)
- Ardeparin (Normiflo)
- Clivarine (Reviparin)

LMWH

- **Less protein binding (>90% bioavailability)**
  - **Each LMWH has different bioavailability and data analyzing one should not be extrapolated**
- **Dosing QD or BID, fixed dose or weight adjusted dose.**

LMWH

- No need to monitor PTT (decreased Thrombin binding)
  - Binds to antithrombin III as a catalyst for anti-factor Xa
- Should monitor anti Xa levels
  - Range .5-1.2
- Side Effects
  - Hemorrhage-4%
  - local irritation at injection site
  - elevated transaminases-5%
  - rare osteopenia or thrombocytopenia
- Contraindicated if h/o HAT

Hirudin/rHirudin

- From saliva of leeches
- Direct thrombin inhibitor
- Lepirudin (Refludan)
  - 0.4 mg/kg bolus with infusion or 0.15 mg/Kg/hr for 2-10 days
- Use if h/o HAT
- Improved RR and overall rate of DVT s/p THR vs LMWH

  NEJM 1997;337(19):1329

Danaparoid

- **Depolymerized mixture of heparin, dermatan sulfate, and chondroitan sulfate**
- **Inhibitor of Factor Xa**
- **750 anti-Xa U BID**
- **$216/day**
- **No PF-4 activity**

Fondaparinux (Arixtra)

- Synthetic Heparin analog
- Factor Xa inhibition with minimal thrombin inhibition
- Does not bind PF-4
- 2.5 mg QD
- $43.50/day
- Avoid if Cr cl<30, Plt <100k, or wt,50 Kg
- Indicated for prophylaxis-THR, hip or knee surgery

Ximelagatran

- **Oral direct Thrombin inhibitor**
- **36 mg BID**
- **No monitoring necessary**

Thrombolytics

- Systemic or catheter directed
- Benefits
  - Preservation of valves (prevent post thrombotic syndrome)
  - Decreased incidence of recurrent DVT (approx. 7%)
- Symptoms < 10 days

Cautions of Outpatient Management

- Must make accurate initial diagnosis
- Assess patient risk factors to explain cause of thrombosis
- Decrease hospitalization does not translate in significant savings
  - increased pressure (utilization & cost) on community services

Prevention

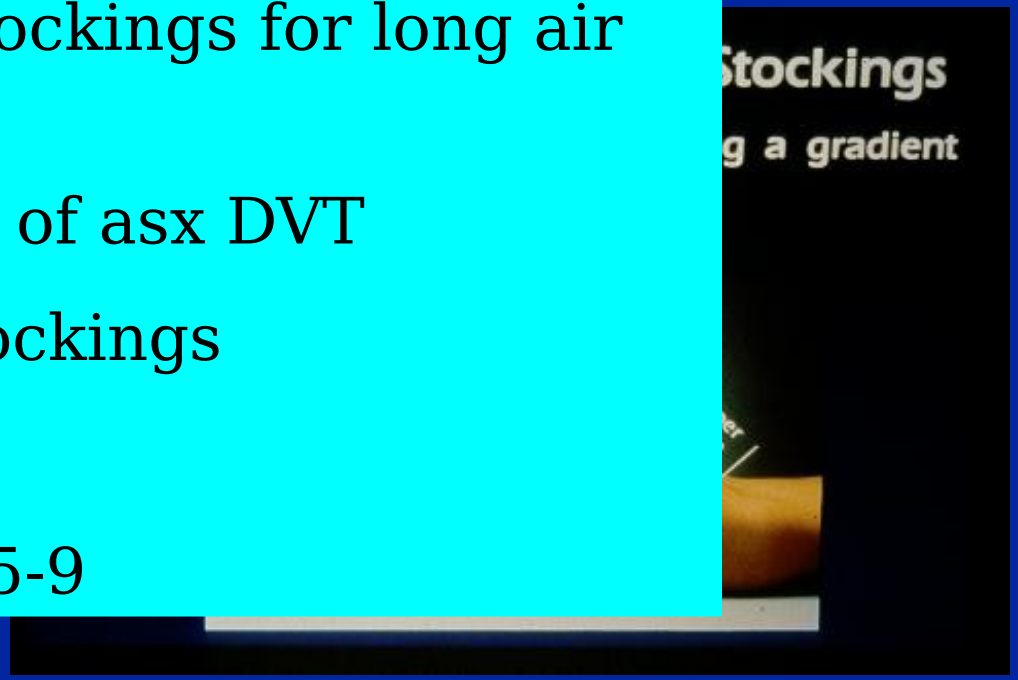
- **Ident**
  high
- **Early**
- **Comp**
  stock
  - **Pne**
  - **Gra**
- **CPM**

Compression Stockings for long air travel

10% prevalence of asx DVT

0 with use of stockings

Lancet 357:1485-9



Prevention

- Heparin
  - Low dose - 5000 units SQ Q12h
- Low-Molecular-Weight Heparin
  - Lovenox (Enoxaparin)- 30 mg SQ Q12h
    - duration 7-10 days
    - antidote = Protamine 1mg for 1mg
    - avg cost $24/day vs. $3 for Heparin
  - Dalteparin (Fragmin)
    - 2500IU (2ml)/day
    - avg cost $14/day

Prevention

- **Xim**
- **? AS**

Ximelagatran

Oral, direct Thrombin inhibitor

Fixed dose 24 mg BID

No monitoring required

Equal efficacy to Coumadin in post op hip & knee pts with a slight increased bleeding risk

Ann Int Med 2002;137:648

IVC Interruption

- **Main objective is to prevent PE**
- **Consideration for high risk patient with anticoagulant complications or failure, i.e. terminal cancer patients or others**

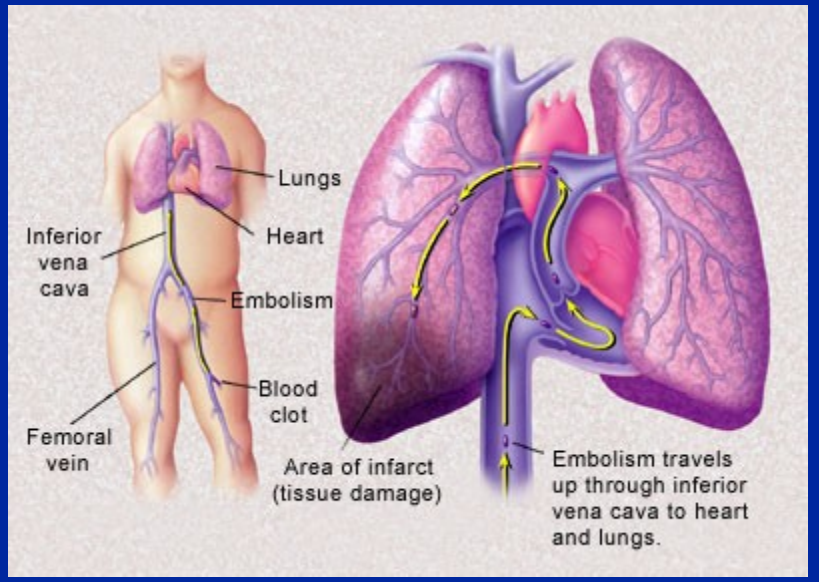
Pulmonary Embolism

Epidemiology

- 300,000 hospitalizations and 100,000-200,000 deaths/year
- Case fatality of 15% (not changed in last decade
- Majority of emboli from deep veins of the lower extremity
- Majority of deaths in undiagnosed

Epidemiology

- PE risk with proximal LE DVT = 50%
- Upper extremity venous thrombosis
  - PE risk = 12-17%
- 70% PE deaths not diagnosed prior to death



Symptoms

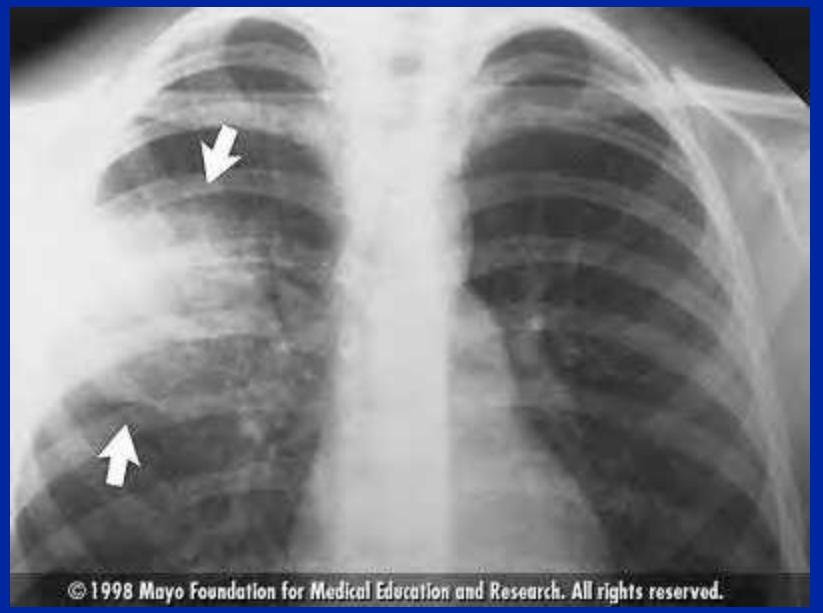
- Dyspnea 81%
- Chest Pain 72%
- Apprehension 59%
- Cough 54%
- Hemoptysis 34%
- Diaphoresis 26%

Physical Findings

- Tachypnea 87%
- Rales 53%
- Loud P2 53%
- Tachycardia 44%
- Fever 42%

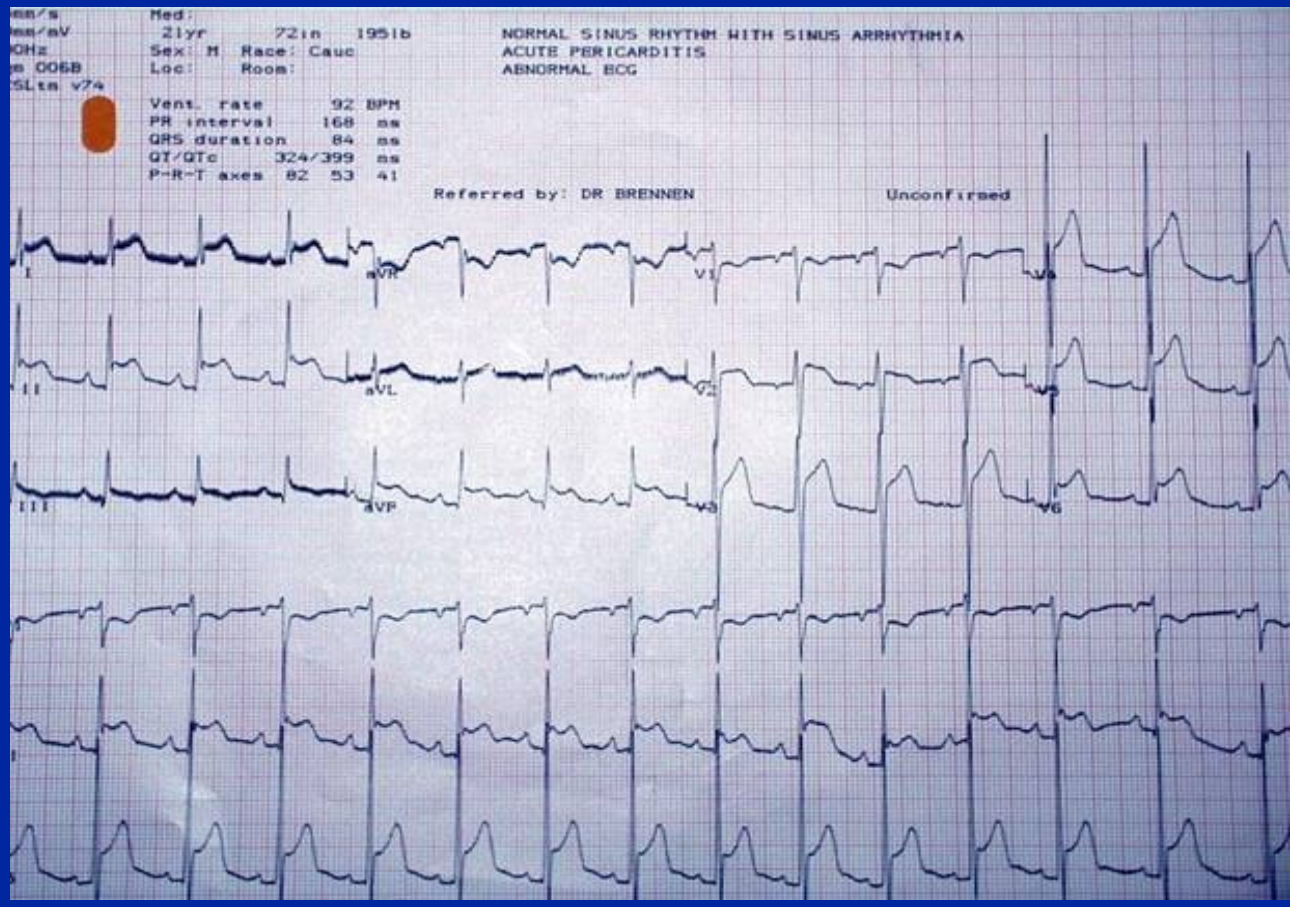
Differential Diagnosis
Pulmonary

- Pneumonia
- COPD/Asthma
- Pneumothorax
- Pleurisy
- Tb
- Cancer



Differential Diagnosis Cardiac

- Myocardial Infarction
- Pericarditis
- CHF
- Tamponade



Differential Diagnosis Musculoskeletal

- Costochondritis
- Rib Fracture
- Myositis
- Trigger Point Pain

Differential Diagnosis Other

- Herpes Zoster
- Sepsis
- Radiation of abdominal pain

Wells PE Criteria

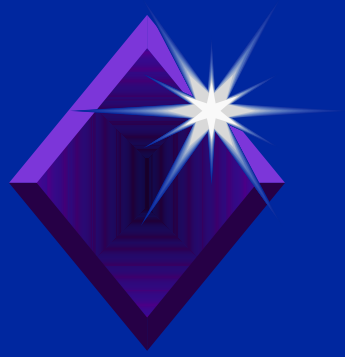
437/930 pts with neg D-dimer and low pres-test prob
1 PE in f/u
NPV=99.5%

Ann Int Med 2001;135:98

<2
2-6
>6

Hemoptysis
1.0

H/o cancer **1.0**



Diagnostic Studies

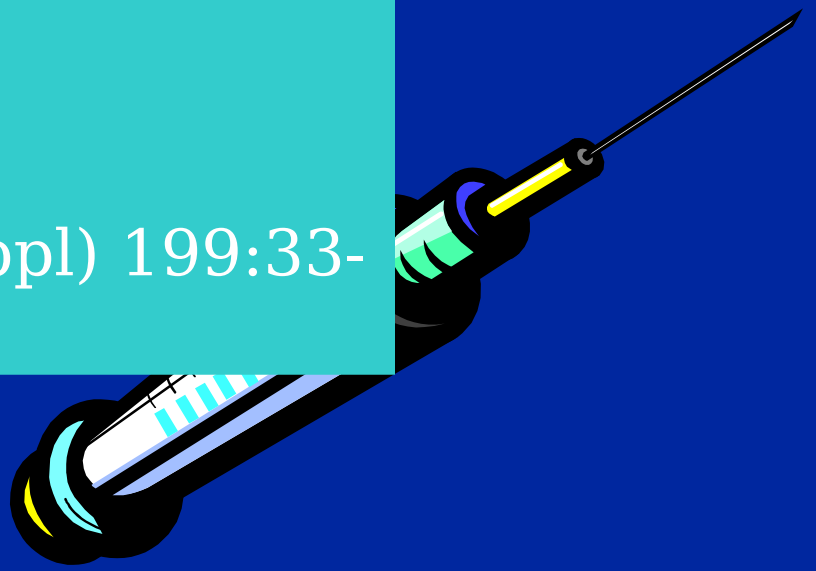
ABG

- **Decrease**
  - **(nl > 80**
- **Increase gradient**
  - **(nl < 20**
- **Decrease CO_2**
  - **(nl > 35 mm Hg)**
- **Low specificity - 29% patients with PE will have all 3 normal**

Negative and PaO2 > 80 mm

NPV 100%

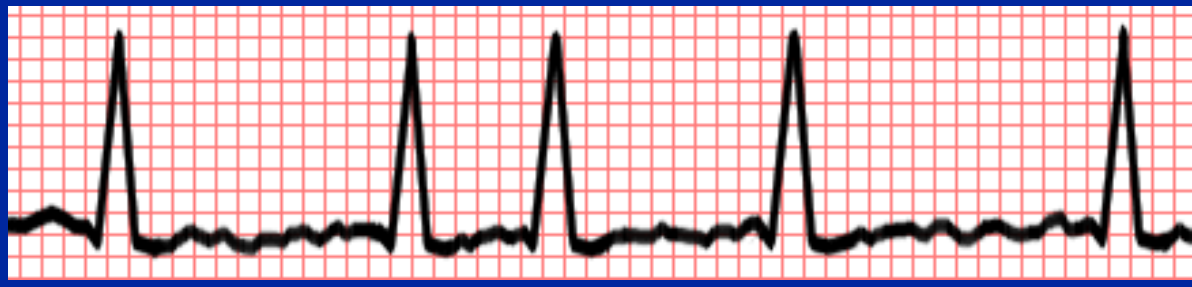
Thorax 54(Suppl) 199:33-36



EKG

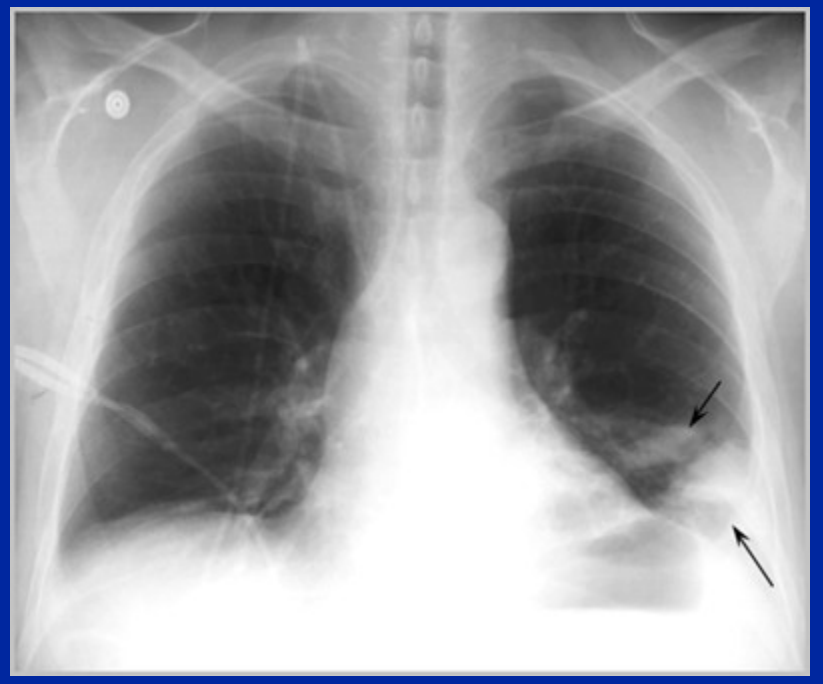
- S1Q3T3
- T wave inversion V1-3
- RV Strain
- Right Axis Deviation
- RBBB
- Atrial arrhythmia (A Fib, Flutter, SVT)

- Most common finding is tachycardia



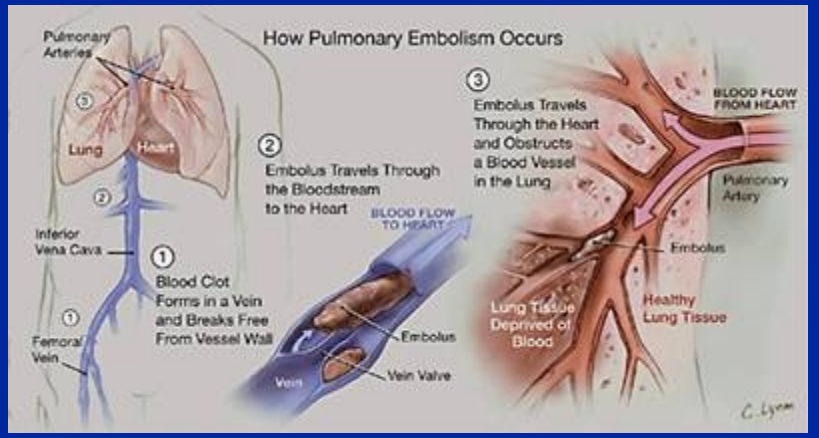
CXR

- Usually normal
- May find:
  - elevated hemidiaphragm
  - focal infiltrates
  - effusion
  - Hampton's Hump (pleural based wedge infiltrate from infarct)



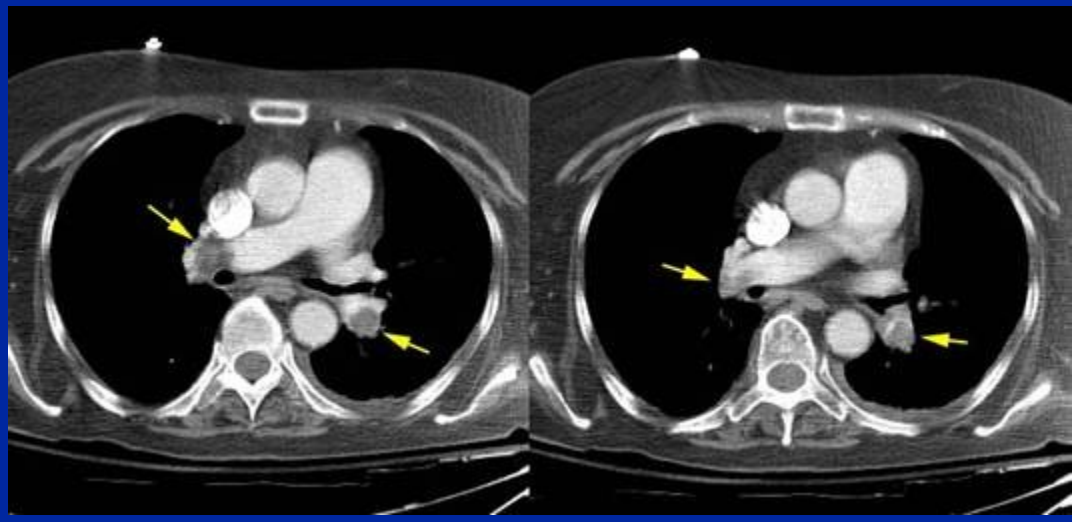
Thoracentesis

- Exudative
- Bloody



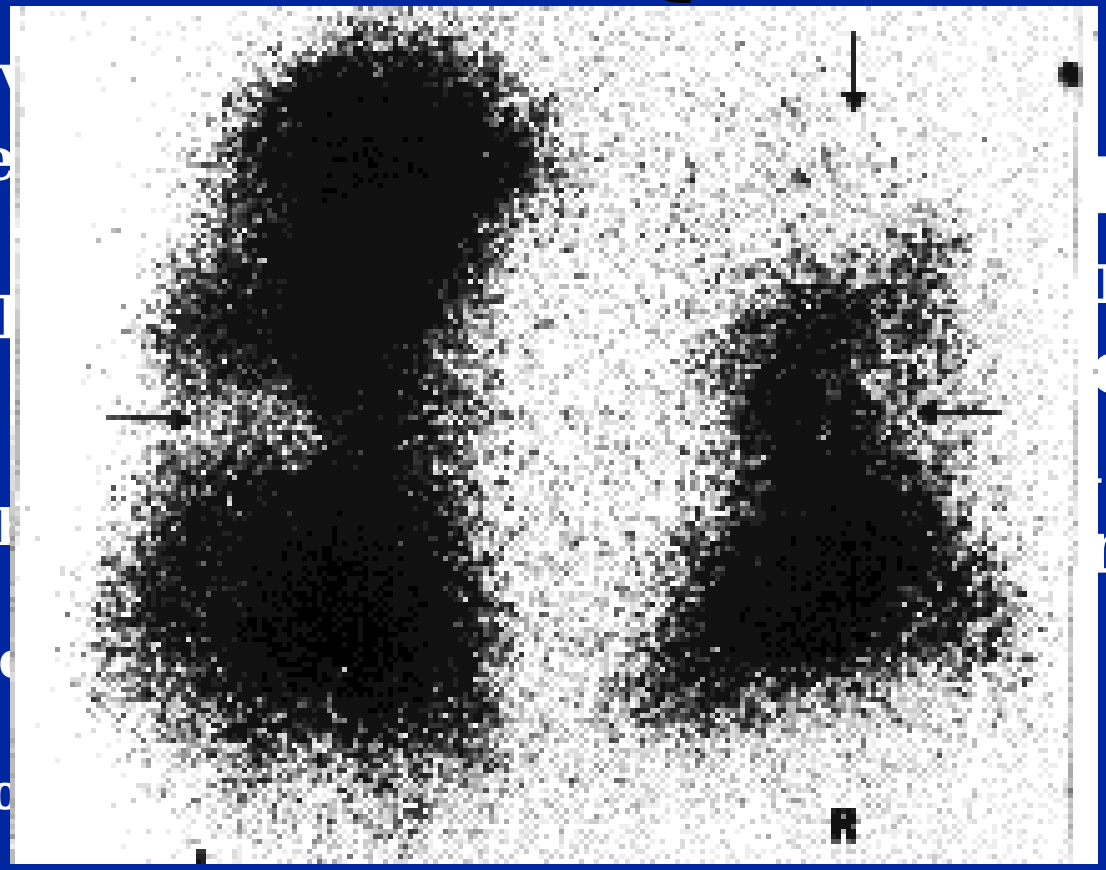
Spiral CT

- Radiology 1996; 201:467-70
- VQ vs. spiral CT in 149 patients
- PAgram done if VQ indeterminate
- Effective in detecting up to segmental level PE
- Sensitivity 82% & 94%
- Specificity 93% & 96%



Ventilation Perfusion Scan (VQ Scan)

- Look for V
  (ventilate
  perfused
- Risk of PI
  - Normal
    0%
  - Low prob
    <10%
  - Intermed
    20-30%
  - High pro
    90%



l PE's
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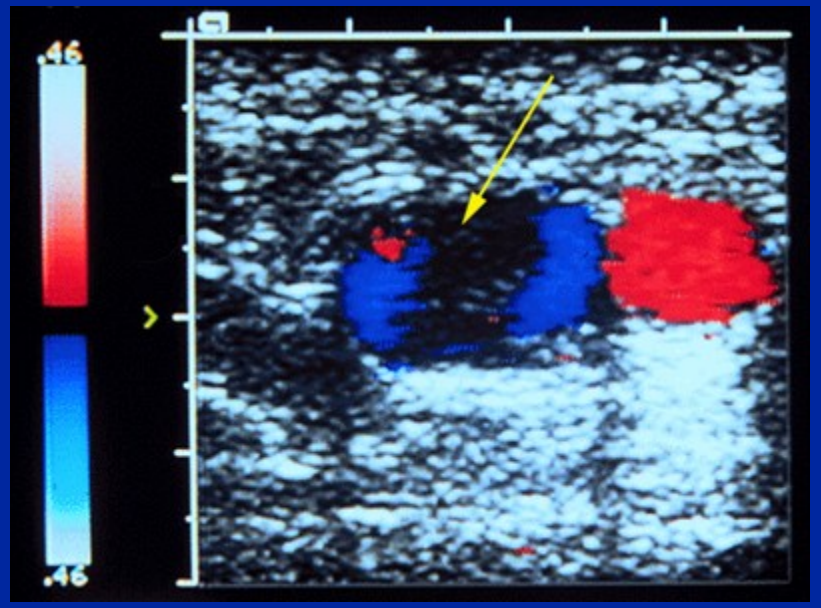
Venography or non-invasive study of the lower extremity

- **Same positive findings as for DVT**
- **Positive LE DVT in a suspicious patient is usually adequate for diagnosis**

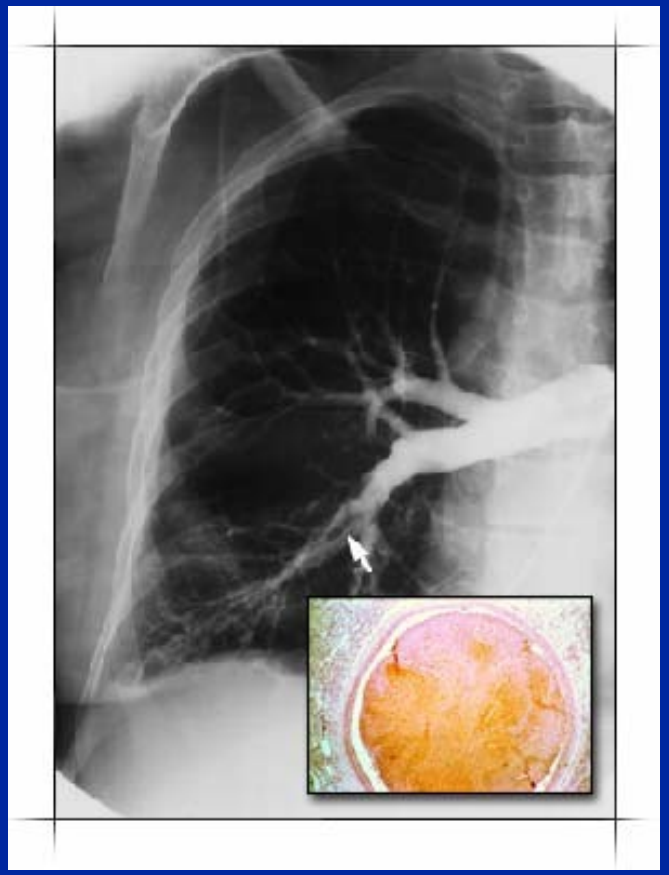


Pulmonary Angiography

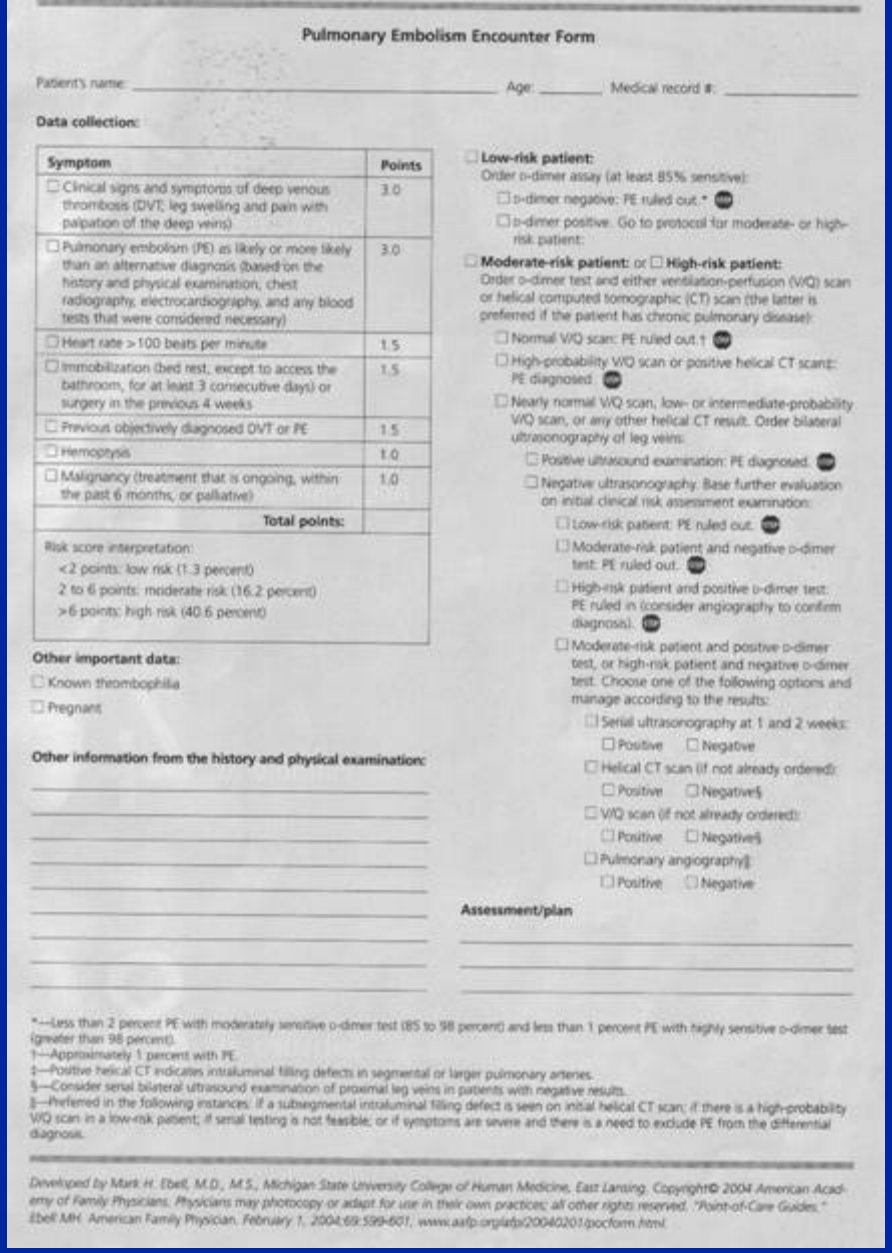
- Gold standard
- Death rate 2-5/1000
- Not widely available
- Consider use if:
  - low prob VQ in suspicious patient
  - consideration for use of thrombolytics
  - contraindication to anticoagulants

MR Angiography

- PAgram vs. MRA with Gadolinium
- Three sets of readings
- Sensitivities 100, 87, & 75%
- Specificities 95, 100, & 95%
- Segmental or larger vessels



NEJM 1997, May 15:1422-27



Pulmonary Embolism Encounter Form

Patient's name: _____ Age: _____ Medical record #: _____

Data collection:

Symptom	Points
☐ Clinical signs and symptoms of deep venous thrombosis (DVT; leg swelling and pain with palpation of the deep veins)	3.0
☐ Pulmonary embolism (PE) as likely or more likely than an alternative diagnosis (based on the history and physical examination, chest radiography, electrocardiography, and any blood tests that were considered necessary)	3.0
☐ Heart rate >100 beats per minute	1.5
☐ Immobilization (bed rest, except to access the bathroom, for at least 3 consecutive days) or surgery in the previous 4 weeks	1.5
☐ Previous objectively diagnosed DVT or PE	1.5
☐ Hemoptysis	1.0
☐ Malignancy (treatment that is ongoing, within the past 6 months, or palliative)	1.0
Total points:	

Risk score interpretation:
<2 points: low risk (1.3 percent)
2 to 6 points: moderate risk (16.2 percent)
>6 points: high risk (40.6 percent)

Other important data:

☐ Known thrombophilia
☐ Pregnant

Other information from the history and physical examination:

_____
_____
_____
_____
_____
_____
_____
_____
_____

☐ **Low-risk patient:**
Order D-dimer assay (at least 85% sensitive):
☐ D-dimer negative: PE ruled out.* END
☐ D-dimer positive. Go to protocol for moderate- or high-risk patient:

☐ **Moderate-risk patient:** or ☐ **High-risk patient:**
Order D-dimer test and either ventilation-perfusion (V/Q) scan or helical computed tomographic (CT) scan (the latter is preferred if the patient has chronic pulmonary disease):
☐ Normal V/Q scan: PE ruled out.† END
☐ High-probability V/Q scan or positive helical CT scan‡: PE diagnosed. END
☐ Nearly normal V/Q scan, low- or intermediate-probability V/Q scan, or any other helical CT result. Order bilateral ultrasonography of leg veins:
☐ Positive ultrasound examination: PE diagnosed. END
☐ Negative ultrasonography. Base further evaluation on initial clinical risk assessment examination:
☐ Low-risk patient: PE ruled out. END
☐ Moderate-risk patient and negative D-dimer test: PE ruled out. END
☐ High-risk patient and positive D-dimer test: PE ruled in (consider angiography to confirm diagnosis). END
☐ Moderate-risk patient and positive D-dimer test, or high-risk patient and negative D-dimer test. Choose one of the following options and manage according to the results:
☐ Serial ultrasonography at 1 and 2 weeks:
☐ Positive ☐ Negative
☐ Helical CT scan (if not already ordered):
☐ Positive ☐ Negative§
☐ V/Q scan (if not already ordered):
☐ Positive ☐ Negative§
☐ Pulmonary angiography‖:
☐ Positive ☐ Negative

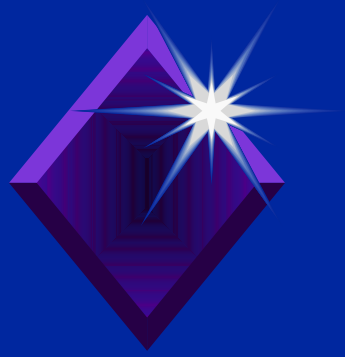
Assessment/plan

_____
_____
_____

*—Less than 2 percent PE with moderately sensitive D-dimer test (85 to 98 percent) and less than 1 percent PE with highly sensitive D-dimer test (greater than 98 percent).
†—Approximately 1 percent with PE.
‡—Positive helical CT indicates intraluminal filling defects in segmental or larger pulmonary arteries.
§—Consider serial bilateral ultrasound examination of proximal leg veins in patients with negative results.
‖—Preferred in the following instances: if a subsegmental intraluminal filling defect is seen on initial helical CT scan; if there is a high-probability V/Q scan in a low-risk patient; if serial testing is not feasible; or if symptoms are severe and there is a need to exclude PE from the differential diagnosis.

Ebell MH. American Family Physician. February 1, 2004;69:599-601. www.aafp.org/afp/20040201pocform.html.

Ebell MH, AFP 2004;69(3):599; FPM Feb 2004; :61



Pre-test Probability

↓

D-dimer

↓

Diagnostic Study

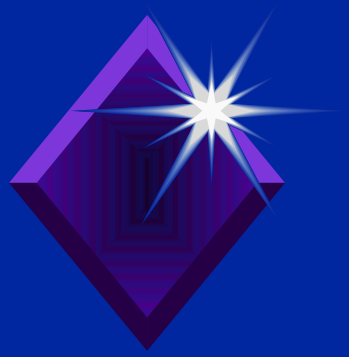
VQ or CT

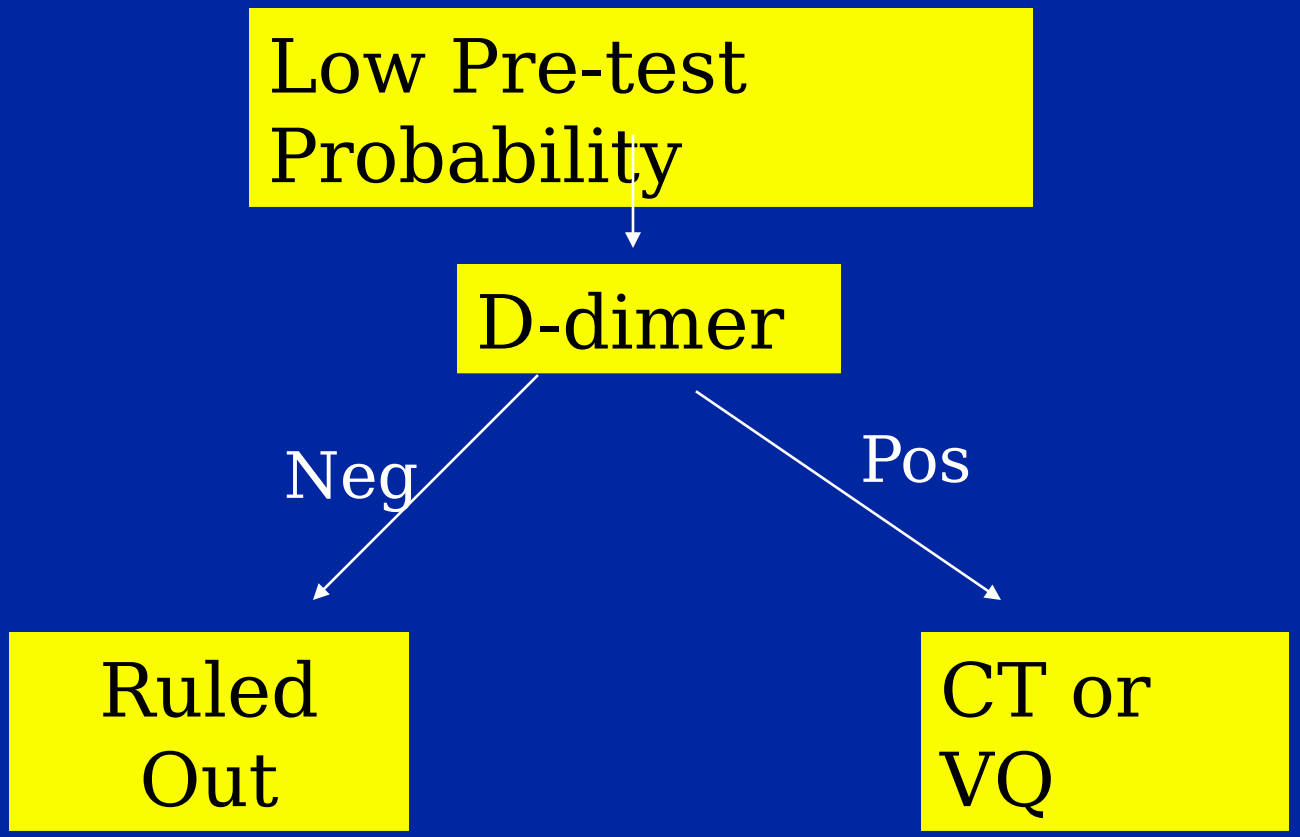
↓

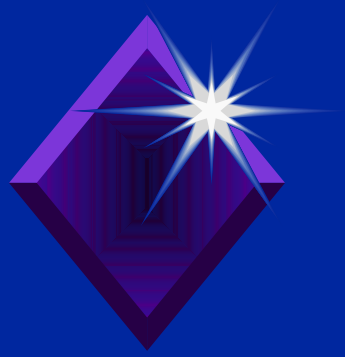
Further Studies

Treat

Follow




Low Pre-test Probability
D-dimer
Neg
Pos
Ruled Out
CT or VQ



High or Intermediate Pre-test Probability

CT or VQ

neg

Ruled Out

pos

Indeterminant Ct or Intermed VQ

Trea t

pos

LE US

neg

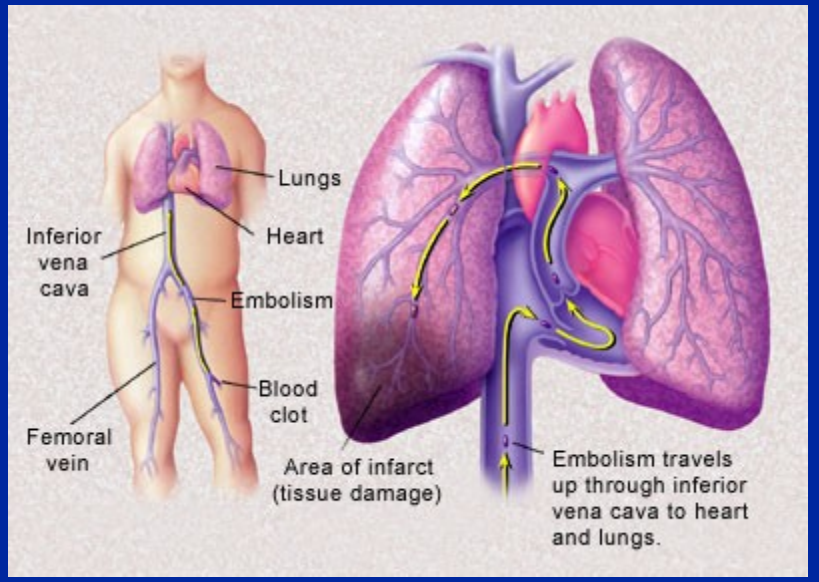
Mod risk & neg D-dimer-ruled out

High risk & pos D-dimer-ruled in

Mod risk and pos D-dimer

Treatment Options

- Anticoagulation
- Thrombolytics



Anticoagulation

- **Prevent further embolization**
- **IV Heparin for 5 days**
  - **Or LMWH**
- **Coumadin starting as early as day 1 Heparin with 4 day overlap**
  - **duration same as for DVT**

Thrombolysis Benefits

- **Accelerated clot lysis and tissue perfusion**
- **Decreased mortality**
- **Reversal of right heart failure**
- **Decreased recurrence**
- **Decrease Pulmonary HTN**

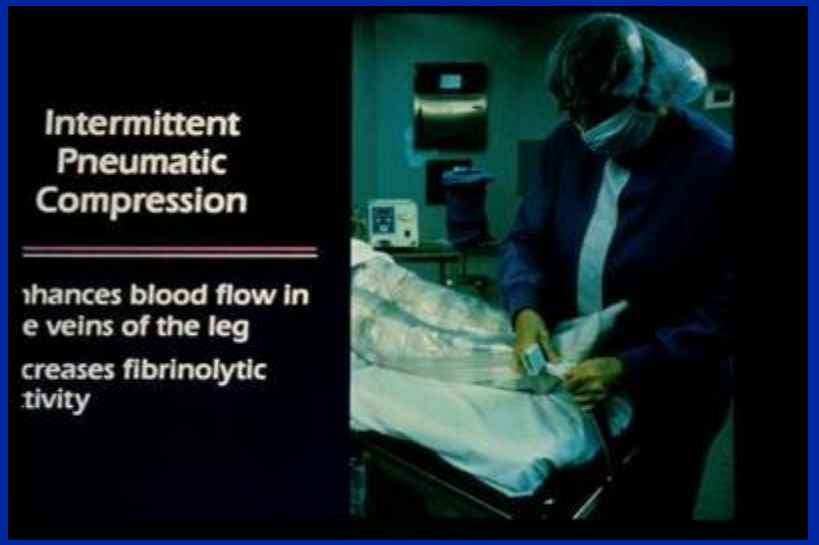
Prognosis

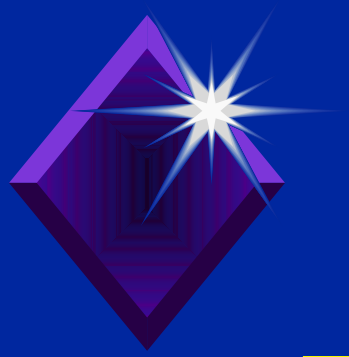
- **If untreated survival is 70% (death 2^{o} recurrent PE)**
- **Treated survival = 92%**
- **Majority of deaths occur before therapy initiated or condition recognized**

Prevention

- Same as for DVT
- Identify high risk patients and institute recommended protocols

WWW.DVT.NET





What to do with the idiopathic DVT?

(Risk of cancer or hypercoagulable state)

Hypercoagulable W/U

- Age < 40
- Thrombus in unusual locations
- Upper extremity, neck, anterior abd wall, eye, CNS
- Recurrent thrombotic events without incident causation
- Recurrent thrombotic events when on anticoagulants in therapeutic range
- Thrombotic events in absence of underlying illness or medication
- Family history of thrombotic events or hypercoagulability
- Bilateral symmetric thrombotic events (bilateral DVT)

Hypercoagulable Labs

- CBC, PT/PTT
- ANA
- Protein C & S
- APC resistance (Factor V Leiden mutation)
- Antiphospholipid antibody
- Antithrombin III
- Fibrinogen & plasminogen
- Prothrombin 20210A Mutation

Risk of cancer?

- Increased risk of discovering cancer in the < 60 age group
- 2/3 adenocarcinoma
  - GI - 25%
  - Urogenital - F12%; M 16%)
  - Hematologic - 10%
- Highest risk in first 6 months
- H&P, CBC,ESR, Chem 20, PSA, Guiac
- NEJM 1998;338:1169
  - 15,348 DVT & 11,305 PE
  - 1737 cancer (est. 1372)

Post Thrombotic Syndrome (Post Phlebitic Syndrome)

Definition

- **Incompetent lower extremity venous valves result in ambulatory venous hypertension**

Findings

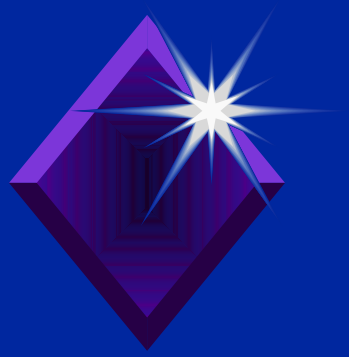
- **Edema**
- **Soft tissue fibrosis**
- **Ulceration**
- **Pain**

Management

- Compression stockings
- Surgical (goal is ulcer healing and decreased pain)
  - Perforator Interruption
    - new laparoscopic technique
  - Valve Repair
    - symptom relief 65%
    - ulcer healing approx. 65% (@5 yrs)

Management

- **Major treatment is prevention of DVT**
- **More aggressive treatment of DVT - Thrombolytics**



Future Trends in Thromboembolism

- Increased use of Low-Molecular-Weight Heparins
  - Approval of newer agents
  - More use in prophylaxis
  - Indications for DVT & PE
  - Outpatient treatment of PE in select patients
- Elimination of Heparin
- Development of Heparin/LMWH alternatives

Future Trends

- **Increased use of thrombolytics for PE and DVT**
  - **catheter directed**
- **Development of better non-invasive or less invasive diagnostic tools**
  - **Magnetic Resonance Venography**
  - **Ultrasound**
  - **Trans-esophageal echo**